

Application No. 10/088,814
 Amendment Dated 12 August 2005
 Reply to Office Action of 14 March 2005

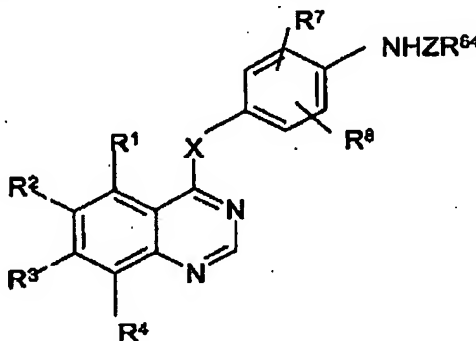
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-19. (Cancelled)

20. (Currently amended) A compound of formula (IIC)



or a salt, ester or amide thereof,

where X is NH , O , or S , $\text{S}(\text{O})$ or $\text{S}(\text{O})_2$, or NR^a where R^a is hydrogen or C_{1-6} alkyl;

Z is $\text{C}(\text{O})$ or $\text{S}(\text{O})_2$;

R^{64} is optionally substituted hydrocarbyl or optionally substituted heterocyclyl optionally substituted aryl selected from phenyl optionally substituted with up to 5 groups selected from nitro, halo, carboxy, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, acetoxy, acetamido, hydroxy, aminosulphonyl, C_{1-4} alkylsulphonyl, trifluoromethyl, arC_{1-10} alkyl, or arC_{1-10} alkoxy wherein aryl rings in the substituents may themselves be substituted with halo, nitro or C_{1-4} alkyl; optionally substituted C_{3-6} cycloalkyl selected from optionally substituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl any of which may be optionally substituted with nitro, halo, carboxy, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, acetoxy, acetamido, hydroxy, aminosulphonyl, C_{1-4} alkylsulphonyl, trifluoromethyl, arC_{1-10} alkyl, arC_{1-10} alkoxy, or aryl wherein aryl rings in the substituents may themselves be substituted with halo, nitro or C_{1-4} alkyl; optionally substituted arC_{1-10} alkyl selected from optionally substituted benzyl, phenylethyl or phenylpropyl, wherein the phenyl ring is optionally substituted with up to 5 groups selected from nitro, halo, carboxy, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, acetoxy, acetamido, hydroxy, aminosulphonyl, C_{1-4} alkylsulphonyl, trifluoromethyl, arC_{1-10} alkyl, or arC_{1-10} alkoxy wherein aryl

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rings in the substituents may themselves be substituted with halo, carboxy, trifluoromethyl, nitro or C₁₋₄alkyl;

optionally substituted heterocyclyl selected from pyridyl, pyrazine, pyrimidinyl, pyrrolidino, furyl, tetrahydrofuryl, oxazolyl, morpholino, thiadiazole, indolyl, quinolinyl, isoquinolinyl, pyrazolyl, methylenedioxybenzyl, thiophene and benzothiophene, all of which may be optionally

substituted with one or more groups selected from nitro, halo, carboxy, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, acetoxy, acetamido, hydroxy, aminosulphonyl, C₁₋₄alkylsulphonyl, trifluoromethyl, arC₁₋₁₀alkyl, or arC₁₋₁₀alkyloxy wherein aryl rings in the substituents may themselves be substituted with halo, carboxy, trifluoromethyl, nitro or C₁₋₄alkyl;

optionally substituted C₁₋₁₀alkyl where optional substituents for C₁₋₁₀alkyl include amino, mono- or di-C₁₋₄alkylamino, hydroxy, C₁₋₄alkoxy, heterocyclyl selected from thiophene,

tetrahydrothiophene-1,1-dioxide, pyrrolidino, morpholino, furyl and tetrahydrofuryl, C₁₋₄alkoxy, acetamido, aryloxy, alkyl(C₁₋₄thio, aroyl where the aryl ring may itself be substituted with halo,

carboxy, trifluoromethyl, nitro, carboxy or trifluoromethyl, C₂₋₁₀cycloalkyl or C₂₋₁₀cycloalkenyl; or optionally substituted C₂₋₁₀alkenyl or C₂₋₁₀alkynyl where optional substituents for C₂₋₁₀alkenyl or

C₂₋₁₀alkynyl include nitro, halo, carboxy, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylthio, acetoxy, acetamido, hydroxy, aminosulphonyl, C₁₋₄alkylsulphonyl, trifluoromethyl, arC₁₋₁₀alkyl, or

arC₁₋₁₀alkyloxy wherein aryl rings in the substituents may themselves be substituted with halo, carboxy, trifluoromethyl, nitro or C₁₋₄alkyl; or such groups are substituted by aryl, where the aryl ring may itself be substituted with halo, nitro, carboxy, trifluoromethyl;

R⁷ and R⁸ are independently selected from hydrogen, halo, C₁₋₄alkyl, C₁₋₄alkoxy,

C₁₋₄alkoxymethyl, di(C₁₋₄alkoxy)methyl, C₁₋₄alkanoyl, trifluoromethyl, cyano, amino, C₂₋₅alkenyl,

C₂₋₅alkynyl, a phenyl group, a benzyl group or a 5-6-membered heterocyclic group with 1-3 heteroatoms, selected independently from O, S and N, which heterocyclic group may be

aromatic or non-aromatic and may be saturated, and [(C)]linked via a ring carbon or nitrogen atom[(D)], or unsaturated, and [(C)]linked via a ring carbon atom[(D)], and which phenyl, benzyl or

heterocyclic group may bear on one or more ring carbon atoms up to 5 substituents selected

from hydroxy, halogeno, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoyloxy, trifluoromethyl, cyano, amino, nitro, C₂₋₄alkanoyl, C₁₋₄alkanoylamino, C₁₋₄alkoxycarbonyl, C₁₋₄alkylsulphonyl, C₁₋₄alkylsulphinyl,

C₁₋₄alkylsulphonyl, carbamoyl, N-C₁₋₄alkylcarbamoyl, N,N-di(C₁₋₄alkyl)carbamoyl, aminosulphonyl, N-C₁₋₄alkylaminosulphonyl, N,N-di(C₁₋₄alkyl)aminosulphonyl,

C₁₋₄alkylsulphonylamino, and a saturated heterocyclic group selected from morpholino,

thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl and pyrazolidinyl, which

saturated heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno,

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C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkanoxy, trifluoromethyl, cyano, amino, nitro and C₁₋₄alkoxycarbonyl, and

where R¹, R², R³ and R⁴ are independently selected from halo, cyano, nitro, trifluoromethyl, C₁₋₃alkyl, -NR¹³R¹⁴, [[Q]]wherein R¹³ and R¹⁴, which may be the same or different, each represents hydrogen or C₁₋₃alkyl[[D]], or -X¹R¹⁵, [[Q]]wherein X¹ represents a direct bond, -O-, -CH₂-, -OCO-, carbonyl, -S-, -SiO-, -SO₂-, -NR¹⁶CO-, -CONR¹⁶-, -SO₂NR¹⁶-, -NR¹⁷SO₂- or -NR¹⁸-, [[Q]]wherein R¹⁶, R¹⁷ and R¹⁸ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl[[D]], and R¹⁵ is selected from one of the following groups:

1') hydrogen or C₁₋₃alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro or amino;

2') C₁₋₃alkylX²COR¹⁹ [[Q]]wherein X² represents -O- or -NR²⁰-, [[Q]]in which R²⁰ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl[[D]], and R¹⁹ represents C₁₋₃alkyl, -NR²¹R²² or -OR²², [[Q]]wherein R²¹, R²² and R²³ which may be the same or different each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl[[D]];

3') C₁₋₃alkylX³R²⁴ [[Q]]wherein X³ represents -O-, -S-, -SO-, -SO₂-, -OCO-, -NR²⁵CO-, -CONR²⁵-, -SO₂NR²⁷-, -NR²⁸SO₂- or -NR²⁹-, [[Q]]wherein R²⁵, R²⁶, R²⁷, R²⁸ and R²⁹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl[[D]], and R²⁴ represents hydrogen, C₁₋₃alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C₁₋₃alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C₁₋₄alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl and C₁₋₄alkoxy[[D]];

4') C₁₋₃alkylX⁴C₁₋₃alkylX⁵R³⁰ [[Q]]wherein X⁴ and X⁵ which may be the same or different are each -O-, -S-, -SO-, -SO₂-, -NR³¹CO-, -CONR³²-, -SO₂NR³³-, -NR³⁴SO₂- or -NR³⁵-, [[Q]]wherein R³¹, R³², R³³, R³⁴ and R³⁵ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl[[D]], and R³⁰ represents hydrogen or C₁₋₃alkyl[[D]];

5') R³⁶ [[Q]]wherein R³⁶ is a 5-6-membered saturated heterocyclic group, [[Q]]linked via carbon or nitrogen[[D]], with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl and C₁₋₄alkylsulphonylC₁₋₄alkyl[[D]];

6') C₁₋₃alkylR³⁶ [[Q]]wherein R³⁶ is as defined in (5') above[[D]];

7') C₂₋₃alkenylR³⁶ [[Q]]wherein R³⁶ is as defined in (5') above[[D]];

8') C₂₋₃alkynylR³⁶ [[Q]]wherein R³⁶ is as defined in (5') above[[D]];

9') R³⁷ [[Q]]wherein R³⁷ represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group, [[Q]]linked via carbon or nitrogen[[D]], with 1-3 heteroatoms selected from O, N

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and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -CONR³⁹R³⁹ and -NR⁴⁰C(OR⁴¹), [(Q)]wherein R³⁹, R³⁹, R⁴⁰ and R⁴¹, which may be the same or different, each represents hydrogen, C₁₋₄alkyl or C₁₋₃alkoxyC₂₋₃alkyl[(D)];

10') C₁₋₆alkylR³⁷ [(Q)]wherein R³⁷ is as defined in (9') above[(D)];

11') C₂₋₆alkenylR³⁷ [(Q)]wherein R³⁷ is as defined in (9') above[(D)];

12') C₂₋₆alkynylR³⁷ [(Q)]wherein R³⁷ is as defined in (9') above[(D)];

13') C₁₋₃alkylX⁶R³⁷ [(Q)]wherein X⁶ represents -O-, -S-, -SO-, -SO₂-, -NR⁴²CO-, -CONR⁴³-, -SO₂NR⁴⁴-, -NR⁴⁵SO₂- or -NR⁴⁶-, [(Q)]wherein R⁴², R⁴³, R⁴⁴, R⁴⁵ and R⁴⁶ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl[(D)], and R³⁷ is as defined hereinbefore[(D)];

14') C₂₋₆alkenylX⁷R³⁷ [(Q)]wherein X⁷ represents -O-, -S-, -SO-, -SO₂-, -NR⁴⁷CO-, -CONR⁴⁸-, -SO₂NR⁴⁹-, -NR⁵⁰SO₂- or -NR⁵¹-, [(Q)]wherein R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰ and R⁵¹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl[(D)], and R³⁷ is as defined in (9') above[(D)];

15') C₂₋₆alkynylX⁸R³⁷ [(Q)]wherein X⁸ represents -O-, -S-, -SO-, -SO₂-, -NR⁵²CO-, -CONR⁵³-, -SO₂NR⁵⁴-, -NR⁵⁵SO₂- or -NR⁵⁶-, [(Q)]wherein R⁵², R⁵³, R⁵⁴, R⁵⁵ and R⁵⁶ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl[(D)], and R³⁷ is as defined hereinbefore[(D)];

16') C₁₋₃alkylX⁹C₁₋₃alkylR³⁷ [(Q)]wherein X⁹ represents -O-, -S-, -SO-, -SO₂-, -NR⁵⁷CO-, -CONR⁵⁸-, -SO₂NR⁵⁹-, -NR⁶⁰SO₂- or -NR⁶¹-, [(Q)]wherein R⁵⁷, R⁵⁸, R⁵⁹, R⁶⁰ and R⁶¹ each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl[(D)], and R³⁷ is as defined hereinbefore[(D)];

and

17') C₁₋₃alkylX⁹C₁₋₃alkylR³⁶ [(Q)]wherein X⁹ and R³⁶ are as defined in (5') above[(D)];

provided that i) where R¹, R⁴, R⁷ and R⁸ are all hydrogen and R² and R³ are both hydrogen or both methoxy, R⁶⁴ is other than phenyl; and

ii) where R¹, R⁴, R⁶, R⁷ and R⁸ are all hydrogen and R² and R³ are methoxy, and Z is C(O), R⁶⁴ is other than methyl; and

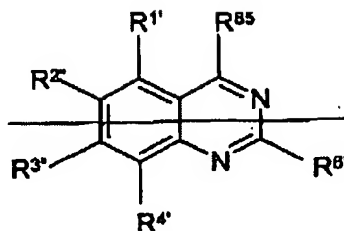
iii) wherein at least one of R¹-R⁴ is -X¹R¹⁶.

to reflect elected sub. matter of Group 15

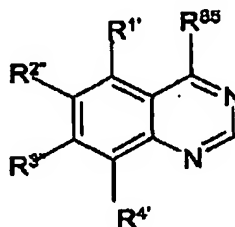
21-26. (Cancelled)

27. (Currently amended) A method for preparing a compound according to claim 2049, which method comprises reacting a compound of formula (VII) [(D)]

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(VIII)



(VII)

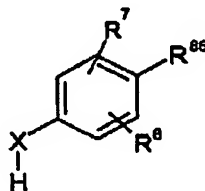
where R^1 is equivalent to the corresponding group of formula R^1 as defined in relation to the said compound of claim 2049, or a precursor thereof;

R^2 is equivalent to the corresponding group of formula R^2 or R^{85} or R^{86} as defined in relation to the said compound of claim 2049, or a precursor thereof;

R^3 is equivalent to the corresponding group of formula R^3 or R^{87} or R^{88} as defined in relation to the said compound of claim 2049, or a precursor thereof;

R^4 is equivalent to the corresponding group of formula R^4 as defined in relation to the said compound of claim 2049, or a precursor thereof;

R^5 is a group R^5 where present in the compound of claim 49, and R^{85} is a leaving group, with a compound of formula (IX')



(IX')

where X, R^7 and R^8 are as defined in relation to the relevant said compound according to claim 20, and R^{88} is a group of formula $NHZR^{84}$ where Z and R^{84} as are defined in the relation to the said compound in claim 2049; and thereafter if desired or necessary converting a group R^1 , R^2 ,

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R^{3'} or R^{4'} to a group R¹, R²-or-R^{2'}-or-R^{6a}, R³-or-R^{3'}-or-R^{6b} and R⁴ respectively or to a different such group.

28-29. (Cancelled)

30. (Currently amended) A pharmaceutical composition comprising a compound of formula (II_{CA}) as defined in claim 2049, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester, or amide thereof, in combination with at pharmaceutically acceptable carrier.

31-33. (Cancelled)

34. (Currently amended) A compound according to claim 20, wherein R^{6a} is phenyl, 2-furan, (E)-CH=CH-phenyl, 3,4,5-trimethoxyphenyl, 2,4-difluorophenyl, 2-nitro-4,5-dimethoxyphenyl, 2,4-dinitrophenyl, 2-fluorobenzyl, cyclopentyl, 1-methylbut-3-enyl, CH₂CH₂ n-heptyl, 2-(methylthio)ethyl, 2-ethoxyethyl, C(CH₃)=CH₂, 5-methyl-2-pyrazine, 3-furyl, 3-cyanophenyl, 4-acetoxyphenyl, 2-nitro-3-methoxyphenyl, 2-methylthiophenyl, 3-acetoxyphenyl, 4-aminosulphenyl, 1-hydroxy-2-naphthyl, 2-pyridyl, 2-quinoliny, 1,5-dimethyl-1H-pyrazolyl, 2-fluoro-5-nitrophenyl, 3-pyridyl, 2-chloro-3-pyridyl, 2-fluorophenyl, 2,3-difluorophenyl, 2,5-difluorophenyl, 2,3-dimethoxyphenyl, 3,5-dimethoxy-4-hydroxy-phenyl, 3-chloro-4-carboxyphenyl, 3-nitro-4-(methylsulphonyl)-phenyl, 3-nitro-4-methoxyphenyl, (E)-CH=CH-(2-nitrophenyl), (E)-CH=CH-(3-nitrophenyl), (E)-CH=CH-(4-nitrophenyl), (E)-CH=CH-(4-chlorophenyl), (E)-CH=CH-(2,3,4-trifluoro-phenyl), (E)-CH=CH-(3-(trifluoromethyl)phenyl), (E)-CH=CH-(4-fluorophenyl), 2-indolyl, 5-fluoro-2-indolyl, 3-fluorophenyl, 3,5-dinitrophenyl, 3-(trifluoromethyl)benzyl, 3-fluorobenzyl, 4-chlorobenzyl, 4-methoxybenzyl, 4-(iso-propyl)benzyl, 3-nitrobenzyl, 2-phenoxyethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(4-chlorobenzoyl)ethyl, 3-chloro-1-propyl, 3-phenoxy-1-propyl, 3-phenyl-1-propyl, 3-benzoylpropyl, dec-9-enyl, 1-methylbut-1-enyl, (2-thiophene)methyl, (3-thiophene)methyl, 2-(3-nitro-4-hydroxyphenyl)ethyl, 3,5-difluorobenzyl, 4-phenylbenzyl, 3,4-methylenedioxybenzyl, 2,6-difluorobenzyl, 4-(n-butoxy)benzyl, 3-methyl-1-butyl, pent-4-ynyl, 3-phenoxybenzyl, 3-(5-bromo-4-methoxy)thiophene, 3-(5-chloro-4-methoxy)-thiophene, 3-methoxy-4-ethoxybenzyl, 4-(benzyloxy)benzyl, 3-(2-thiophene)propyl, hex-5-ynyl, 1-(4-chlorophenyl)cyclopropyl, cyclopentylmethyl, 2-(cyclopentyl)ethyl, cyclohexylmethyl, 2-(cyclohexyl)ethyl, 3-(cyclohexyl)propyl, 1-phenoxyethyl, (E)-C(CH₃)=CH-phenyl, 2-chloro-5-nitrophenyl, methyl, n-heptyl, 2-furyl, 3-furyl, (2-thiophene)methyl, 2-Indolyl.

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2,4-difluorophenyl, (3-nitro-4-(methylsulphonyl))-phenyl, pent-4-ynyl, 5-methyl-2-pyrazinyl, cyclopentyl, (cyclohexyl)methyl, 3-nitro-4-methoxyphenyl, 2-tetrahydrofuryl, 2-pyridyl, 3-pyridyl, (E)-CH=CH-(4-nitrophenyl), 1,5-dimethyl-pyrazol-3-yl, cyclobutyl, 2-methoxyphenyl, 3-nitrophenyl, 4-nitrophenyl, cyclohexyl, 4-nitropyrrol-2-yl, 3-nitro-4-methylphenyl, 3-nitro-4-fluorophenyl, (3-thiophene)methyl, 3-chloro-2-benzothiophene, 5-chloro-2-indolyl, (1-piperidine)ethyl, 3,4-methylenedioxyphenyl, but-3-ynyl, 3-cyanophenyl, 2-(acetamido)ethyl, 4-(trifluoromethyl)phenyl, 3-chloro-4-fluorophenyl, 4-fluoro-3-(trifluoromethyl)-phenyl, 4-fluorophenyl, 5-bromo-2-thiophene, 4-methoxyphenyl, 6-methyl-3-pyridyl, 5-nitro-2-furyl, 2-nitrophenyl, (E)-CH=CH-(3-chlorophenyl), 2-thiophene, cyclopropyl, 3-methylphenyl, 2-chlorophenyl, 2-fluorophenyl, 2,5-dichlorophenyl, 3-fluorophenyl, 6-chloro-3-pyridyl, 5-bromo-2-furyl, 3-nitro-2-methylphenyl, 3-chlorophenyl, 3-(tetrahydrothiophene-1-1'-dioxide)methyl, 2-methoxyethyl, or 2-(methylthio)phenyl.

35. (Previously presented) A compound according to claim 20, where R^{6a} is phenyl or halosubstituted phenyl.

36. (Currently amended) A compound according to claim 2033, where R¹ is hydrogen and R⁴ is halo, C₁₋₄alkyl or C₁₋₄alkoxy.

37. (Currently amended) A compound according to claim 2033, where X¹ is oxygen.

38. (Currently amended) A compound according to claim 2033, where R¹⁵ is selected from a group (1'), (3'), (6') or (10') as defined in claim 204.

39. (Currently amended) A compound according to claim 2033, where R⁷ and R⁸ are independently selected from hydrogen, halo, C₁₋₄alkoxy, cyano, trifluoromethyl or phenyl.

40. (Currently amended) An *in vivo* hydrolysable ester of a compound according to claim 2033, which is a phosphate ester.

41. (New) A compound according to claim 20 where R¹ is hydrogen, R⁴ is halo, C₁₋₄alkyl or C₁₋₄alkoxy, X¹ is oxygen, R¹⁵ is selected from a group (1'), (3'), (6') or (10') as defined in claim 20 and R⁷ and R⁸ are independently selected from hydrogen, halo, C₁₋₄alkoxy, cyano, trifluoromethyl or phenyl.

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42. (New) A compound according to claim 41 where R^{6a} is phenyl or halosubstituted phenyl.
43. (New) A compound according to claim 34 wherein R^1 is hydrogen, R^4 is halo, C_{1-4} alkyl or C_{1-4} alkoxy, X^1 is oxygen, R^{15} is selected from a group (1'), (3'), (6') or (10') as defined in claim 20 and R^7 and R^8 are independently selected from hydrogen, halo, C_{1-4} alkoxy, cyano, trifluoromethyl or phenyl.
44. (New) A method of treating colorectal or breast cancer in a warm blooded animal in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (IC), as claimed in claim 20.